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LEVOTHYROXINE REPLACEMENT THERAPY FOR LEFT VENTRICULAR DIASTOLIC DYSFUNCTION IN PATIENTS WITH SUBCLINICAL HYPOTHYROIDISM

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ABSTRACT
Background: Subclinical hypothyroidism (SH) has been associated with abnormal echocardiographic parameters and left ventricular diastolic dysfunction (LVDD). We aimed to evaluate left ventricular function and determine the efficacy of levothyroxine (L-T4) replacement therapy on LVDD in patients with SH.
Materials and Methods: Ninety-five women with SH (83 F, age 41±10 yrs) and 44 healthy women (39 F, age 39±10 yrs) were included. Thyroid profile and echocardiographic examinations were performed on all subjects. L-T4 therapy was initiated to patients with SH who were diagnosed with LVDD (n=25). Echocardiographic measurements were repeated at 6 months of treatment.
Results: Peak early diastolic filling velocity (E) and time-to-peak filling rate (E/A) were significantly lower, while interventricular septal thickness at end-diastole (IVSD) and left ventricular end-diastolic diameter were significantly higher in the SH group. The E/A and IVSD showed improvement in SH patients receiving L-T4 treatment at 6 months compared to baseline.
Conclusion: We conclude that L-T4 replacement therapy may reverse left ventricular dysfunction and IVSD observed in SH patients and suggest that treatment should be advised to prevent the alteration of myocardial function.

KEYWORDS: Levothyroxine, thyroid stimulating hormone, hypothyroidism, left ventricular dysfunction, echocardiography

LIST OF ABBREVIATIONS:
A: Peak late diastolic filling velocity
DBP: Diastolic blood pressure
E: Peak early diastolic filling velocity
E/A: Time-to-peak filling rate
FS: Fractional shortening
LVDd: Left ventricular end-diastolic diameter
LVDs: Left ventricular end-systolic diameter
IVSD: Interventricular septal thickness at end-diastole
L-T4: Levothyroxine
LVDD: Left ventricular diastolic dysfunction
SBP: Systolic blood pressure
SH: Subclinical hypothyroidism
T3: Triiodothyronine
T4: Thyroxine
TSH: Thyroid stimulating hormone.Levothyroxine Replacement Therapy for Left Ventricular Diastolic Dysfunction in patients with Subclinical Hypothyroidism

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INTRODUCTION

Subclinical hypothyroidism (SH), also refered as mild hypothyroidism, is defined as an elevated thyroid stimulating hormone (TSH) level associated with a normal serum free thyroxine (T4) concentration (Biondi and Cooper, 2008). The prevalence of SH was reported to be 4-10% in adults, reaching up to 20% in elderly women (Biondi and Cooper, 2008, Canaris *et al*., 2000, Hollowell *et al*. 2002). Thyroid hormones have direct and indirect effects on the heart and vascular system and overt hypothyroidism is a known cardiovascular risk factor (Klein and Ojamaa, 2001). Although less certain, SH is also associated with abnormal cardiac function. Left ventricular diastolic dysfunction (LVDD), which is an early sign of heart failure, is the best established effect of SH (Aghini-Lombardi *et al.*2006, Biondi *et al*. 1999, Brenta *et al.*, 2003, Monzani *et al*., 2001, Yazici *et al*., 2004, Di Bello *et al*., 2000, Vitale *et al*., 2002). In addition, reduced systolic function (especially with effort), decreased cardiac preload and increased systemic vascular resistance was also reported (Faber *et al.*, 2002, Ripoli *et al.*, 2005). Some epidemiological studies suggest that SH may contribute to the development of atherosclerosis and coronary heart disease, though no association has been found with cardiovascular or overall mortality (Cappola *et al*., 2006, Hak *et al*., 2000, Walsh *et al*., 2005). Several studies have investigated the efficacy of L-T4 replacement therapy in reversing cardiac abnormalities and other subtle symptoms SH, but there is still controversy on whether patients with SH require treatment (Villar *et al*., 2007).

In the present study, we aimed to evaluate left ventricular function in patients with SH and determine the efficacy of L-T4 replacement therapy in patients with LVDD.

MATERIALS AND METHODS

This study was conducted at the Endocrinology Outpatient Clinic of Haseki Training and Research Hospital between 2003 and 2005. Ninety-five patients with SH and 44 sex- and age-matched healthy controls (n=44) were included in the study. Diagnosis of SH was based upon a TSH level >4.67 µIU/ml with T3 and T4 hormones within normal ranges. SH diagnosis was made 12±3 months before enrollment. TSH and fT4 measurements were repeated in order to establish the diagnosis. Subtotal thyroidectomy was performed for Graves disease and multinodular goiter in 43 of the patients with SH, and 52 of the patients had Hashimoto's thyroiditis. Subjects did not have any preexisting conditions that could cause left-ventricular dysfunction and did not use any medication interfering with left ventricular function. Following laboratory analysis and echocardiographic measurements, SH patients diagnosed with LVDD (n=25) were initiated on L-T4 replacement therapy (L-T4 treatment group). L-T4 dose was adjusted to maintain TSH levels within the normal range (0.49–4.67 µIU/ml). The mean dose of L-T4 was 130±64 µg/day. Only five patients required more than 100 µg of L-T4 per day. No side effects were reported. Normal TSH values were achieved in 6-8 weeks of treatment. After maintenance of euthyroid state for 6 months, echocardiographic measurements were repeated in the group treated with L-T4. Study was approved by the Local Ethics Committee and informed consent was obtained from all participants.

Physical examination was performed and detailed medical history of all participants was recorded. Fasting blood samples were collected, centrifuged for 10 min at 2500 x g, and stored at -20ºC until analysis. TSH and free T4 levels were determined using chemiluminescent assay (Immulite 2000, BioDPC, Los Angeles, CA, USA) according to the manufacturer's instructions. The normal reference ranges for TSH and free T4 were 0.49-4.67 µIU/ml and 0.7-1.49 ng/mL, respectively.

All echocardiographic evaluations were performed in accordance with American Echocardiography Association Guideline (18). Echocardiography was performed on all subjects at the beginning of the study and repeated after maintenance of euthyroid state for 6 months in the L-T4-treated group. All subjects had echo Doppler evaluation in the left lateral decubitus position.

M-mode and two-dimensional (2D) echocardiograms and Doppler analysis (Sonos 1000, Hewlett-Packard Co., Palo Alto, CA; equipped with a 2.5- or 3.5-MHz transducer) were performed in all subjects. 2D images were obtained in parasternal long axis and short axis views and apical two- and four-chamber views using standard transducer positions. M-mode echocardiographic tracings were used to measure left ventricular end- diastolic diameter (LVDd), fractional shortening percentage, end diastolic septal and posterior wall thickness. Left ventricular diastolic filling was assessed in supine position at three stages [resting, immediately after exercise (within the first minute), and within 3-5 minutes of cessation of exercise] using 2D guided transmitral, pulsed-

wave Doppler echocardiography. The following indices of left ventricular diastolic filling were determined at all three stages: Peak early diastolic filling velocity (E) (cm/sec), peak late diastolic or atrial (A) filling velocity (cm/sec), and peak E/A ratio. LVDD was diagnosed if E/A-ratio < 1.

Statistical analysis was performed using SPSS version 11.0. Descriptive statistics are expressed as mean ± standard deviation (SD). Non-parametric Mann Whitney U test was used for comparison of means between SH and control groups. Student's t test was used for before and after treatment comparison of means within the L-T4 treatment subgroup. Pearson test was used for correlation analysis. A p value <0.05 was considered statistically significant.

RESULTS

Ninety-five patients with SH (83 women; mean age 41±10 years) and 44 age and gender-matched healthy controls (39 women; mean age, 39±10 years) were included in the study. There was no significant difference between the groups in terms of gender, age and blood pressure levels. Mean TSH levels were 19.58±19.75 µIU/ml in the SH group and 1.49±0.96 µIU/ml in the control group (Table 1). Thyroid autoantibodies (anti thyroid peroxidase [anti TPO], antithyroglobulin [anti Tg] were positive in 54.73% of SH patients.

Table 1. Clinical and hormonal characteristics of subjects in study groups.

	SH (n=95)	Control (n=44)	p value
Age (years)	41±10	39±10	NS
Sex (F/M)	83/12	39/5	NS
SBP (mm Hg)	121.8±21.7	117.5±17.8	NS
DBP (mm Hg)	79.7±14.8	76.1±11.4	NS
TSH (µIU/ml)	*19.58±19.75*	*1.49±0.96*	*<0.0001*
Free T4 (ng/ml)	*1.11±0.15*	*1.03±0.22*	*NS*

Data are presented as mean ± SD. SH, subclinical hypothyroidism; SBP, systolic blood pressure; DBP, diastolic blood pressure; TSH, thyroid stimulating hormone; free T3, free triiodothyronine; free T4, free thyroxine; NS, not significant.

Echocardiographic results for SH and control groups are presented in Table 2. The mean E (0.83±0.25 vs. 0.99±0.17, p<0.0001) and E/A ratios (1.18±0.33 vs. 1.33±0.23, p=0.003) of SH patients were significantly lower than the values observed in the control group. Interventricular septal thickness at end-diastole (IVSd, 0.98±0.12 vs. 0.91±0.08, p=0.001) and left ventricular end-systolic diameter (LVESD, 4.53±0.46 vs. 4.35±0.39, p=0.025) were significantly higher in the SH group compared to control group. Fractional shortening, a measure of right ventricular systolic function, was not affected in SH patients. In Pearson correlation analysis, TSH levels were positively correlated with IVSD (r=0.194, p=0.031) in both groups.

Table 2. Echocardiographic results of study groups at baseline.

	SH (n=95)	Control (n=44)	p value
E (m/s)	0.83±0.25	0.99±0.17	<0.0001
A (m/s)	0.81±0.32	0.76±0.18	0.313
E/A	1.18±0.33	1.33±0.23	0.003
IVSD (mm)	0.98±0.12	0.91±0.08	0.001
LVDs (cm)	4.53±0.46	4.35±0.39	0.025
LVDd (cm)	2.86±0.30	2.81±0.41	0.494
FS (%)	38.47±4.00	39.80±4.77	0.091

Data are presented as mean ± SD. SH, subclinical hypothyroidism; E, peak early diastolic filling velocity; E/A, time-to-peak filling rate; A, peak late diastolic filling velocity; IVSD, interventricular septal thickness at end diastole; LVDs, left ventricular end-systolic diameter; LVDd, left ventricular end-diastolic diameter; FS, fractional shortening.

Within the SH group, 25 patients (26% of the SH group) were diagnosed with LVDD and consequently were started on thyroid replacement therapy. No significant difference was found between the SH patients with and without LVDD regarding the mean TSH values (18.28±15.48 µIU/ml and 12.88±18.85 µIU/ml, respectively; p>0.05). After achieving normal TSH values (0.49-4.67 µIU/ml), L-T4 treatment was continued for 6 months. Patients were compliant with the treatment and did not report any side effects. Comparison of echocardiographic results before and after treatment showed significant differences in E/A and IVSD measurements. E/A ratio increased from 0.75±0.23 (pretreatment) to1.09±0.22 (Post-treatment), while IVSD decreased from 1.05±0.14 mm (pretreatment) to 0.95±0.10 mm (Post-treatment) (p<0.0001, for both) (Table 3).

Table 3. Echocardiographic results of SH patients at baseline and after treatment

	Pretreatment (n=25)	(Post-treatment), (n=25)	p value
E (m/s)	0.57±0.21	0.77±0.26	<0.02
A (m/s)	0.76±0.15	0.70±0.18	0.19
E/A	0.75±0.23	1.09±0.22	0.0001
IVSD (mm)	1.05±0.14	0.95±0.10	0.0001
LVDs (cm)	4.66±0.45	4.67±0.33	0.89
LVDd (cm)	2.90±0.28	2.86±0.24	0.39
FS (%)	39.44±3.75	41.52±2.90	0.002

Data are presented as mean ± SD. E, peak early diastolic filling velocity; A, peak late diastolic filling velocity; E/A, time-to-peak filling rate; IVSD, interventricular septal thickness at end-diastole; LVDs, left ventricular end-systolic diameter; LVDd, left ventricular end-diastolic diameter; FS, fractional shortening

DISCUSSION

In this study, we determined that mean E and E/A ratio were lower, while mean septal thickness and end-systolic diameter were higher in SH patients compared to controls. An improvement in the echocardiographic parameters were observed in the repeat echocardiogram performed in SH patients with LVDD after 6 months of treatment.

Left ventricular diastolic dysfunction was reported to present as prolonged isovolumic relaxation time in several studies (Aghini-Lombardi *et al.*, 2006, Biondi *et al*, 1999, Monzani *et al.*, 2001, Yazici *et al*., 2004, Di Bello *et al*. 2000, Vitale *et al*. 2002, Quinones *et al.*, 2002). Most, but not all of these studies also reported a decrease in E/A ratio, not associated with an increase in A (Biondi *et al.*, 1999, Yazici *et al*., 2004, Mishra *et al*., 2005, Franzoni *et al*, 2006). Only Franzoni et al. (2006), reported a decrease in E along with an increase in A (20). In contrast, we observed a significant decrease in E together with a non-significant increase in A. Moreover, IVSD was significantly greater in patients with SH compared to controls in our study, while no change was observed in the other studies (Biondi *et al.*, 1999, Mishra *et al*., 2005, Monzani *et al*., 2001, Yazici *et al*. 2004, Franzoni *et al*, 2006). These discrepancies may be related to patient selection criteria, age differences, or underlying etiology.

Whether SH patients should be treated with L-T4 or monitored until conversion to overt hypothyroidism is open to debate. However, SH may carry the similar cardiovascular risks as overt hypothyroidism. A recent meta-analysis of 10 population based studies found a risk ratio of 1.20 for coronary heart disease, 1.18 for cardiovascular mortality and 1.12 for total mortality (Ochs *et al*., 2008). The risk ratio for coronary heart disease was higher among people younger than 65 years (RR, 1.51). Many authors, especially North American Cardiologists, but also endocrinologists prefer not to treat SH patients, particularly older patients because of increased cardiovascular risk.

In the present study we limited ourselves at diagnosis and treatment of LVDD in SH patients, and found that reaching euthyroidism improved left ventricular function in this patient population. LVDD is not only a prognostic factor preceding heart failure, but isolated LVDD is also associated with increased morbidity and mortality in the general population (Zile and Brutsaert, 2002). Several studies investigated the efficacy of L-T4 treatment on cardiac abnormalities using conventional and tissue Doppler echocardiography (Biondi *et al.*, 1999, Yazici *et al*., 2004, Mishra *et al*., 2005, Franzoni *et al*, 2006, Arinc *et al*., 2006, Mariotti *et al*. 2008) and

by other techniques such as video densitometry (Brenta *et al.*, 2003, Monzani *et al.*, 2001) or magnetic resonance imaging (Ripoli *et al*., 2005). Consistent with our results, all of the above studies detected left ventricular dysfunction and reported reversal of abnormalities by L-T4 treatment, regardless of the diagnostic method. A 2007 Cochrane review of 12 randomized controlled trials comparing L-T4 treatment to placebo or no treatment also concluded that L-T4 replacement could improve some parameters of left ventricular function and lipid profile in patients with SH (Villar *et al*., 2007).

In conclusion, L-T4 replacement therapy may reverse left ventricular dysfunction and IVSD and should be advised to prevent the alteration of myocardial function in patients with SH.

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